REMARKS/ARGUMENTS

I. Support for Claim Amendments

Applicants thank the Examiner for the thoughtful comments and suggestions in the October 24, 2006, Office Action.

Applicants have amended claim 1 to recite a step of "contacting the subject's isolated brain tissue with a nucleic acid probe which is at least 95% complementary to mRNA encoding FGFR2." Support for this claim may be found in the specification at paragraphs 72-75 (describing methods of hybridizing identical and substantially identical nucleic acids); at paragraphs 112-127 (describing hybridization techniques for detecting levels of mRNA expression); paragraph 229 (describing microarray analysis using Affymetrix chips to detect genes identified in Table 4, including FGFR2); and Table 5 (confirming results using RT-PCR to measure mRNA expression). Claim 1 has also been amended to change the phrase, "determining whether a subject is predisposed ..." to "determining the likelihood that a subject has major depression disorder." Support for this amendment may be found in the specification at, *e.g.*, paragraphs 86 and 224. Lastly, claim 1 has been amended to recite the term "probe" rather than "reagent." Support for this amendment may be found throughout the specification, but especially at paragraphs 86 and 115 (describing the use of nucleic acid probes for detecting mRNA expression).

New claim 31 depends from claim 1 and is limited to methods wherein "said nucleic acid probe is fully complementary to mRNA encoding FGFR2." Support for this claim may be found in the specification at paragraphs 72-75 (describing methods of hybridizing identical and substantially identical nucleic acids); at paragraphs 112-127 (describing hybridization techniques for detecting levels of mRNA expression); paragraph 229 (describing microarray analysis using Affymetrix chips to detect genes identified in Table 4, including FGFR2); and Table 5 (confirming results using RT-PCR to measure mRNA expression).

Claim 30, drawn to methods of determining the likelihood that a *deceased* subject had major depression disorder, has been canceled and rewritten as new claim 32. New claim 32

otherwise recites all the limitations of claim 1 and finds support in the same sections of the specification as identified for claim 1, as well as the Examples, *e.g.*, paragraph 229. New claim 33 depends from claim 32 and is limited to methods wherein "said nucleic acid probe is fully complementary to mRNA encoding FGFR2." Claim 33 is supported by the same sections of the specifications listed for claim 31, above.

No new matter is added by any of the forgoing amendments to the claims.

II. Rejection of Claims under 35 U.S.C. § 112, paragraph 1, enablement

On page 2 of the Office Action, the Examiner rejected claims 1 and 30 under 35 U.S.C. § 112, paragraph 1 as non-enabled. Specifically, the Examiner states the following:

> [T]he specification, *while being enabling for detecting expression of human FGFR2 receptor nucleic acid in the dorsolateral prefrontal cortex of a deceased patient and concluding that the patient had major depression disorder*, does not reasonably provide enablement for determining if the patient is predisposed to depression. (emphasis added)

With respect to the emphasized language, Applicants' new claims 32 and 33 represent a sincere attempt to draft allowable claims drawn to this embodiment.

On pages 3-5 of the Office Action, the Examiner argues that Applicants' claims are not enabled for embodiments drawn to determining whether a patient "has an inclination or higher likelihood of developing a mental disorder when compared to an average person in the general population." The Examiner derives this limitation from Applicants' use of the term "predisposed" in the previously pending claims. As discussed above, Applicants have deleted the phrase "predisposed" from each of their pending claims. The claimed methods are now drawn to methods of *determining the likelihood that a subject has major depression disorder.* As such, the claims describe methods which may be utilized to collect information that is useful for diagnosing or confirming a diagnosis of major depression disorder. Specifically, the information collected relates to presence of diminished levels of FGFR2 mRNA in the subject's dorsolateral prefrontal cortex compared to the level observed in normal patients. The information can be used in conjunction with other methods of diagnosing major depression disorder to determine that a patient is *more likely* to have (or to have had) major depression

disorder than not and, as part of the determination, the results and implications can be reported or recorded for future reference.

Applicants' amendments to claim 1 address the issues raised by the Examiner with respect to the previous recitation of the "predisposed." Moreover, Applicants' specification enables the pending claims because postmortem brain expression patterns relate reasonably well to expression patterns in living brains and the techniques required to practice Applicants' invention do not require undue experimentation on the part of those skilled in the art (on the contrary, the techniques are standard).

As discussed in the previous Office Action, the Federal Circuit has held that Applicants are required to show that the art recognizes a *reasonable* correlation between a model (*e.g.*, post-mortem brains) and the claimed method, not a "rigorous" or "invariable" correlation. *See Cross v. Itzuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also* MPEP 2164.02. Applicants provided evidence which satisfies this requirement in the previous Office Action. Applicants' arguments in this regard are strengthened further by virtue of the fact that the present amendment has substantially narrowed the scope of the pending claims. As demonstrated in the specification, MDD is associated with reduced levels of FGFR2 mRNA expression in the DLPFC. *See, e.g.*, Figure 4 (showing at least 50% decrease in levels of expression of FGFR2 in MDD subjects versus subjects patients). Applicants' claimed methods exploit this relationship to obtain information that is relevant to determining the likelihood that a subject has major depression disorder, or died suffering from the disease.

III. Rejection of Claims under 35 U.S.C. § 112, paragraph 1 (indefiniteness)

On page 5 of the October 24, 2006 Office Action, the Examiner rejected claims 1 and 30 for failing to meet the written description requirement of 35 U.S.C. § 112, paragraph 1 (*i.e.*, indefiniteness). Specifically, the Examiner objected to the term "selectively associates," which was Applicants' attempt to functionally define how the nucleic acid "reagents" recited in Applicants' claims recognized FGFR2 mRNA and allowed the mRNA to be quantitated. The Examiner suggested on page 5 of the Office Action that the pending claims be amended so "that the probe or 'nucleic acid reagent' to be used have a requisite degree of identity with SEQ ID

NO:1." The Examiner explained that such an amendment would address the lack of recitation in the claims of "any particular structure" for the "reagent."

Applicants have amended their claims to address the Examiner's rejection. First, as discussed above, Applicants have amended the claims to refer to "probes" rather than "reagents." The term "probe" is well-known in the art and refers to molecules which bind with high specificity to target molecules in a population such that the target molecules can be selectively detected and/or measured. Applicants have also amended the claims to recite a particular structure for the probes: the probes in independent claims 1 and 32 are at least 95% complementary to FGFR2 mRNA; the probes in dependent claims 31 and 33 are 100% complementary to FGFR2 mRNA. Applicants respectfully submit that this language, in the context of the claimed methods as a whole and the specification, provides sufficient structural clarity for one of skill in the art to discern the scope of the invention.

On page 5 of the specification, the Examiner also objected to the term "selectively associates" and argued that Applicants had not provided any evidence as to the "precise definition" of "selectively." Applicants are not certain how much "precision" the Examiner is demanding. In the context of the modern era of molecular biology, the use of complementary nucleic acid probes for selectively detecting the presence of a target nucleic acid is ancient and extremely well-understood. In light of the claimed methods (amended to recite a definite structure for the nucleic acid probes) and the specification (describing numerous methods of detecting specified target mRNA using nucleic acid probes) the term "selectively associates" clearly refers to the highly specific binding of the probe to its target (in this case, FGFR2 mRNA). In this context, Applicants are not aware of any other reasonable interpretation of the term that might confuse a skilled artisan who was willing to understand what Applicants are claiming.

On page 7 of the Office Action, the Examiner objected to the term "significantly less than the control." Specifically, the Examiner stated:

> The term "significantly less than the control" in claim 1 part (iv) is a relative term which renders the claim indefinite. The term ... is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary

> skill in the art would not be reasonably apprised of the scope of the invention. It is unclear when a difference between a control and experimental sample might be considered significant. It could be a 1% change, a 10% change, or a 50% change. It is not clear whether the artisan is to determine significance in his or her own mind or alternatively whether a statistically significant difference must be present.

Applicants have removed the term "significantly," without prejudice, in a sincere attempt to address the Examiner's rejection. As Applicants have pointed out above and elsewhere, the claims -- *when read in light of the specification* -- are clear. In contrast, Applicants are not sure what the Examiner means when the Examiner states, "it is not clear whether the artisan is to determine significance in his or her own mind." The key feature of this step, as would be understood by any skilled artisan reading the claim, is the determination made when the observed levels of FGFR2 mRNA in the test subject are *less than* those observed in a control subject (*e.g.*, a subject of similar age and physiology who is *not* suffering from major depression disorder), and *reproducibly* so, *i.e.*, the differences observed are outside the range of error of the instrumentation used to make the measurements. Applicants believe any skilled artisan would understand this fundamental point without it being expressly (and trivially) recited in the claims or in the specification.[1]

The decreased levels of expression of FGFR2 mRNA in the DLPFC of subjects suffering from major depression disorder is plainly taught by the specification, *e.g.*, in Tables 1-5. Moreover, Figure 4 and 14 present the observed fold-changes of various genes (expressed in log (base 2) form typical of expression arrays), including FGFR2. Thus, the specification shows that the reduction of FGFR2 in the DPFLC of subjects with major depression disorder is readily and reproducibly detectable (*e.g.*, expression is at least 25-50% of that observed in normal subjects). One skilled in the art reading the claims in light of this teaching would readily understand what

[1] Again, Applicants remind the Examiner that 35 U.S.C. § 112 does not require Applicants to teach the skilled practitioner what the skilled practitioner already knows ("a patent need not teach, and preferably omits, what is well known in the art"). *See* MPEP 2164.01 (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Likewise, it is not necessary for Applicants' to specify every sub-step in the method(s) of practicing the invention if it is known to one skilled in the art that such information could be obtained without undue experimentation. *See* MPEP 2164.01(c); see also MPEP 2164.02 (citing *In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970)).

is claimed. There is absolutely no need for the practitioner to rely on definitions made-up "in his or her own mind," as suggested by the Examiner.

For all the forgoing reasons, Applicants respectfully submit that their pending claims satisfy the definiteness requirement of 35 U.S.C. § 112, paragraph 1.

IV. Rejection of Claims under 35 U.S.C. § 112, paragraph 1 (new matter)

On page 6 of the Office Action (specifically, paragraph 7), the Examiner argues that Applicants' claims, as earlier amended, incorporate new matter. Specifically, the Examiner objected to the language in the claims which referred to the use of nucleic acid reagents "which bind to sequences at least 95% identity to SEQ ID No. 1." The Examiner states that support can not be found "for using a nucleic acid reagent which binds to sequences which are variants of SEQ ID NO:1." The Examiner notes, however, that the amendments suggested in the Office Action at paragraph 5 "may ... obviate this rejection."

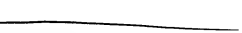
As discussed above, Applicants have essentially followed the Examiner's suggestion and amended the claims to identify the probes *structurally*. Applicants' claims recite the use of probes which are "at least 95% complementary to mRNA encoding FGFR2." The meaning of this phrase and the purpose of these probes within the context of the claimed method could not be more plain to those of skill in the art. Applicants' respectfully submit that the specification supports the use of probes with at least 95% complementarity to FGFR2 mRNA, as probes meeting this structural criterion and which are useful for detecting FGFR2 mRNA are easily identified by one of skill in the art. For example, it is well-known that some probes which lack complementarity at their 5' or 3' ends recognize their target with a binding specificity nearly equal to that of a fully complementary probe. Applicants' claims address this fact, and the specification discusses probe selection and methods of nucleic acid hybridization at length, *e.g.*, at pages 28-32 ("IV. Detection of Gene Expression"). For all the forgoing reasons, Applicants respectfully submit that the "new matter" rejection raised by the Examiner (relating to the detection of "variants" of) is mooted by the claim amendments presented herein.

CONCLUSION

Applicants again gratefully acknowledge the Examiner's careful review of their claims and specification. During the course of prosecuting this application, Applicants have substantially narrowed their claims in an effort to find common ground with the Examiner and to address the merits of the Examiner's rejections and objections. In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner has a question about the claims or believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000. At this stage in prosecution, Applicants have found that the few remaining issues can often be efficiently resolved by a formal interview.

Respectfully submitted,



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